1. NAME OF THE MEDICINAL PRODUCT

Abacavir Tablets USP 300mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains abacavir sulfate, USP equivalent to 300 mg of abacavir

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dosage from: Tablet

Description: Yellow colored, biconvex, capsule shaped, film coated tablets debossed with 'H' on one side and '139' on other side separating 13 & 9 with score line

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abacavir tablets, USP in combination with other antiretroviral agents, are indicated for the treatment of human immunodeficiency virus (HIV-1) infection

4.2 Posology and method of administration

Therapy-naive Adults

CNA30024 was a multicenter, double-blind, controlled trial in which 649 HIV-1-infected, therapy-naive adults were randomized and received either abacavir (300 mg twice daily), lamivudine (150 mg twice daily), and Efavirenz (600 mg once daily); or zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and Efavirenz (600 mg once daily). The duration of double-blind treatment was at least 48 weeks. Trial participants were: male (81%), white (51%), black (21%), and Hispanic (26%). The median age was 35 years; the median pretreatment CD4+ cell count was 264 cells per mm3, and median plasma HIV-1 RNA was 4.79 log10 copies per mL. The outcomes of randomized treatment are provided in Table 1

Outcome	**Abacavir plus Lamivudine plus Efavirenz (n = 324)**	**Zidovudine plus Lamivudine plus Efavirenz (n = 325)**
Responder[a]	69% (73%)	69% (71%)
Virologic failures[b]	6%	4%
Discontinued due to adverse	14%	16%

reaction[s]		
Discontinued due to other reason[s]	10%	11%

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 209 cells per mm3 in the group receiving abacavir and 155 cells per mm3 in the zidovudine group. Through Week 48, 8 subjects (2%) in the group receiving abacavir (5 CDC classification C events and 3 deaths) and 5 subjects (2%) on the zidovudine arm (3 CDC classification C events and 2 deaths) experienced clinical disease progression.

CNA3005 was a multicenter, double-blind, controlled trial in which 562 HIV-1-infected, therapy-naive adults were randomized to receive either abacavir (300 mg twice daily) plus COMBIVIR® (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times a day) plus COMBIVIR twice daily. The trial was stratified at randomization by pre-entry plasma HIV-1 RNA 10,000 to 100,000 copies per mL and plasma HIV-1 RNA greater than 100,000 copies per mL. Trial participants were male (87%), white (73%), black (15%), and Hispanic (9%). At baseline the median age was 36 years; the median baseline CD4+ cell count was 360 cells per mm3, and median baseline plasma HIV-1 RNA was 4.8 log10 copies per mL. Proportions of subjects with plasma HIV-1 RNA less than 400 copies per mL (using Roche AMPLICOR HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Table 2.

[a] subjects achieved and maintained confirmed HIV-1 RNA less than or equal to 50 copies per mL (less than 400 copies per mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR® standard test 1 PCR).

[b] includes viral rebound, insufficient viral response according to the investigator, and failure to achieve confirmed less than or equal to 50 copies per mL by Week 48.

[c] includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

Outcomes of Randomized Treatment through Week 48 (CNA3005)

Outcome	**Abacavir plus Lamivudine/Zidovudine (n = 262)**	**Indinavir plus Lamivudine/Zidovudine (n = 262)**
Responder[a]	49%	50%
Virologic failure[b]	31%	28%
Discontinued due to adverse	10%	12%

reactions Discontinued due to other reasons[c]	11%	10%

[a] Subjects achieved and maintained confirmed HIV-1 RNA less than 400 copies per mL.

[b] Includes viral rebound and failure to achieve confirmed less than 400 copies per mL by Week 48.

[c] Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

Treatment response by plasma HIV-1 RNA strata is shown in Table3.

Table3 Proportions of Responders through Week 48 by Screening Plasma HIV-1 RNA Levels (CNA3005)

Screening HIV-1 RNA (copies/mL)	**Abacavir plus Lamivudine/Zidovudine (n = 262)**		**Indinavir plus Lamivudine/Zidovudine (n = 265)**	
	<400 copies/mL	**n**	**<400 copies/mL**	**n**
>10,000 - <100,000	50%	166	48%	165
>100,000	48%	96	52%	100

In subjects with baseline viral load greater than 100,000 copies per mL, percentages of subjects with HIV- 1 RNA levels less than 50 copies per mL were 31% in the group receiving abacavir versus 45% in the group receiving indinavir.

Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells per mm3 was observed in both treatment arms. Through Week 48, 9 subjects (3.4%) in the group receiving abacavir (6 CDC classification C events and 3 deaths) and 3 subjects (1.5%) in the group receiving indinavir (2 CDC classification C events and 1 death) experienced clinical disease progression.

CNA30021 was an international, multicenter, double-blind, controlled trial in which 770 HIV-1-infected, therapy-naive adults were randomized and received either abacavir 600 mg once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once daily and Efavirenz 600 mg once daily. The double-blind treatment duration was at least 48 weeks. Trial participants had a mean age of 37 years; were male (81%), white (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells per mm3 (range 21 to 918 cells per mm3) and the median baseline plasma HIV-1 RNA was 4.89 log10 copies per mL (range: 2.60 to 6.99 log10 copies per mL).

The outcomes of randomized treatment are provided in Table 4.

Table 4 Outcomes of Randomized Treatment through Week 48 (CNA30021)

Outcome	**Abacavir 600 mg q.d. plus EPIVIR® plus Efavirenz (n = 384)**	**Abacavir 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386)**
Respondera	64% (71%)	65% (72%)
Virologic failureb	11% (5%)	11% (5%)
Discontinued due to adverse reactions	13%	11%
Discontinued due to other reasons[c]	11%	13%

[a] subjects achieved and maintained confirmed HIV-1 RNA less than 50 copies per mL (less than400 copies per mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR standard test version 1).

[b] includes viral rebound, failure to achieve confirmed less than 50 copies per mL (less than 400 copies per mL) by Week 48, and insufficient viral load response.

[c] includes consent withdrawn, lost to follow up, protocol violations, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 188 cells per mm3 in the group receiving abacavir 600 mg once daily and 200 cells per mm3 in the group receiving abacavir 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group receiving abacavir 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%) in the group receiving abacavir 300 mg twice daily (7 CDC classification C events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed to trial medications.

Pediatric Trials

Therapy-experienced Pediatric Subjects

CNA3006 was a randomized, double-blind trial comparing abacavir 8 mg per kg twice daily plus lamivudine 4 mg per kg twice daily plus zidovudine 180 mg per m2 twice daily versus lamivudine 4 mg per kg twice daily plus zidovudine 180 mg per m2 twice daily. Two hundred and five therapy-experienced pediatric subjects were enrolled: female (56%), white (17%), black (50%), Hispanic (30%), median age of 5.4 years, baseline CD4+ cell percent greater than 15% (median = 27%), and median baseline plasma HIV-1 RNA of 4.6 log10 copies per mL. Eighty percent and 55% of subjects had prior therapy with zidovudine and lamivudine, respectively, most often in

combination. The median duration of prior nucleoside analogue therapy was 2 years. At 16 weeks the proportion of subjects responding based on plasma HIV-1 RNA less than or equal to 400 copies per mL was significantly higher in subjects receiving abacavir plus lamivudine plus zidovudine compared with subjects receiving lamivudine plus zidovudine, 13% versus 2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 log10 copies per mL in the group receiving abacavir plus lamivudine plus zidovudine compared with -0.21 log10 copies per mL in the group receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were 69 cells per mm3 in the group receiving abacavir plus lamivudine plus zidovudine and 9 cells per mm3 in the group receiving lamivudine plus zidovudine.

4.3 Contraindications

Abacavir tablet is contraindicated in patients:

• who have the HLA-B*5701 allele

• with prior hypersensitivity reaction to abacavir.

• with moderate or severe hepatic impairment

4.4 Special warnings and precautions for use

Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir. These hypersensitivity reactions have included multi-organ failure and anaphylaxis and typically occurred within the first 6 weeks of treatment with abacavir (median time to onset was 9 days); although abacavir hypersensitivity reactions have occurred any time during treatment [see Adverse Reactions (6.1)]. Patients who carry the HLA-B*5701 allele are at a higher risk of abacavir hypersensitivity reactions; although, patients who do not carry the HLA- B*5701 allele have developed hypersensitivity reactions. Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with abacavir-containing products where HLA- B*5701 screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when subjects carrying the HLA-B*5701 allele were excluded. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision making.

Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with abacavir:

- All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with abacavir or reinitiation of therapy with abacavir, unless patients have a previously documented HLA-B*5701 allele assessment.

- Abacavir tablets are contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.
- Before starting abacavir tablets, review medical history for prior exposure to any abacavir-containing product. NEVER restart abacavir tablets or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status.
- To reduce the risk of a life-threatening hypersensitivity reaction, regardless of HLA-B*5701 status, discontinue abacavir immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).
- If a hypersensitivity reaction cannot be ruled out, do not restart abacavir tablets or any other abacavir-containing products because more severe symptoms which may include life-threatening hypotension and death can occur within hours.
- If a hypersensitivity reaction is ruled out, patients may restart abacavir. Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life-threatening reactions within hours of reinitiating abacavir therapy. Therefore, reintroduction of abacavir tablets or any other abacavir-containing product is recommended only if medical care can be readily accessed.
- A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretroviral. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering abacavir to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with abacavir should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including abacavir. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Myocardial Infarction

In a published prospective, observational, epidemiological trial designed to investigate the rate of myocardial infarction (MI) in patients on combination antiretroviral therapy, the use of abacavir within the previous 6 months was correlated with an increased risk of MI. In a sponsor-conducted pooled analysis of clinical trials, no excess risk of MI was observed in abacavir-treated subjects as compared with control subjects. In totality, the available data from the observational cohort and from clinical trials are inconclusive.

As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking).

4.5 Interaction with other medicinal products and other forms of interaction

No studies on the effects on ability to drive and use machines have been performed.

4.6 Pregnancy and lactation

Pregnancy: Teratogenic effects:

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to abacavir during pregnancy. Physicians are encouraged to register patients by calling the Antiretroviral Pregnancy Registry at 1-800-258-4263.

Risk Summary

Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects for abacavir compared with the background rate for major birth defects of 2.7% in the US reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). Abacavir produced fetal malformations and other embryonic and fetal toxicities in rats at 35 times the human exposure at the recommended clinical dose. The relevance of animal findings to human pregnancy registry data is not known.

Data

Human Data: Based on prospective reports from the Antiretroviral Pregnancy Registry of over 2,000 exposures to abacavir during pregnancy resulting in live births (including over 900 exposed in the first trimester), there was no difference between abacavir and overall birth defects compared with the background birth defect rate of 2.7% in the US reference population of the MACDP. The prevalence of defects in the first trimester was 3% (95% CI: 2% to 4.4%).

Animal Data: Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced crown-rump length) were observed in rats at a dose which produced 35 times the human exposure based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of the potential for HIV-1 transmission, mothers should be instructed not to breastfeed.

Pediatric Use

The safety and effectiveness of abacavir have been established in pediatric patients aged 3 months and older. Use of abacavir is supported by pharmacokinetic trials and evidence from adequate and well-controlled trials of abacavir in adults and pediatric subjects

Geriatric Use Clinical trials of abacavir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of abacavir in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Impaired Hepatic Function

A dose reduction is required for patients with mild hepatic impairment (Child-Pugh Class A) [see Dosage and Administration The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate or severe hepatic impairment; therefore, abacavir is contraindicated in these patients

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed.

4.8 Undesirable effects

The following adverse reactions are discussed in other sections of the labeling:

- Serious and sometimes fatal hypersensitivity reactions
- Lactic acidosis and severe hepatomegaly with steatosis
- Immune reconstitution syndrome
- Fat redistribution
- Myocardial infarction

Clinical Trials Experience in Adult Subjects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Serious and Fatal Abacavir-associated Hypersensitivity Reactions

In clinical trials, serious and sometimes fatal hypersensitivity reactions have occurred with abacavir [see Boxed Warning, Warnings and Precautions (5.1)]. These reactions have been characterized by 2 or more of the following signs or symptoms: (1) fever; (2) rash; (3) gastrointestinal symptoms (including nausea, vomiting, diarrhea, or abdominal pain); (4) constitutional symptoms (including generalized malaise, fatigue, or achiness); (5) respiratory symptoms (including dyspnea, cough, or pharyngitis). Almost all abacavir hypersensitivity reactions include fever and/or rash as part of the syndrome.

Other signs and symptoms have included lethargy, headache, myalgia, edema, arthralgia, and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, myolysis, and death have occurred in association with these hypersensitivity reactions. Physical findings have included lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and maculopapular or urticarial rash (although some patients had other types of rashes and others did not have a rash). There were reports of erythema multiforme. Laboratory abnormalities included elevated liver chemistries, elevated creatine phosphokinase, elevated creatinine, and lymphopenia, and abnormal chest x-ray findings (predominantly infiltrates, which were localized).

Additional Adverse Reactions with Use of Abacavir

Therapy-naive Adults: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or equal to 5% frequency during therapy with abacavir 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily from CNA30024 are listed in Table 5

Table 5. Treatment-emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4, Greater than or Equal to 5% Frequency) in Therapy-naive Adults (CNA30024[a]) through 48 Weeks of Treatment

Adverse Reaction	**Abacavir plus Lamivudine plus Efavirenz (n = 324)**	**Zidovudine plus Lamivudine plus Efavirenz (n = 325)**
Dreams/sleep disorders	10%	10%
Drug hypersensitivity	9%	<1%[b]
Headaches/migraine	7%	11%
Nausea	7%	11%
Fatigue/malaise	7%	10%
Diarrhea	7%	6%
Rashes	6%	12%
Abdominal pain/gastritis/ gastrointestinal signs and symptoms	6%	8%

Depressive disorders	6%	6%
Dizziness	6%	6%
Musculoskeletal pain	6%	5%
Bronchitis	4%	5%
Vomiting	2%	9%

[a] This trial used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the trial, suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 subjects in the abacavir group and 3% of 325 subjects in the zidovudine group.

b Ten (3%) cases of suspected drug hypersensitivity were reclassified as not being due to abacavir following unblinding.

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or equal to 5% frequency during therapy with abacavir 300 mg twice daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from CNA3005 are listed in Table 6

Table.6 Treatment-emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4, Greater than or Equal to 5% Frequency) in Therapy-naive Adults (CNA3005) through 48 Weeks of Treatment

Adverse Reaction	**Abacavir plus Lamivudine/Zidovudine (n = 262)**	**Indinavir plus Lamivudine/Zidovudine (n = 264)**
Nausea	19%	17%
Headache	13%	9%
Malaise and fatigue	12%	12%
Nausea and vomiting	10%	10%
Hypersensitivity reaction	8%	2%
Adverse Reaction	**Abacavir plus Lamivudine/Zidovudine (n = 262)**	**Indinavir plus Lamivudine/Zidovudine (n = 264)**
Diarrhea	7%	5%

Fever and/or chills	6%	3%
Depressive disorders	6%	4%
Musculoskeletal pain	5%	7%
Skin rashes	5%	4%
Ear/nose/throat infections	5%	4%
Viral respiratory infections	5%	5%
Anxiety	5%	3%
Renal signs/symptoms	<1%	5%
Pain (non-site-specific)	<1%	5%

Five subjects receiving abacavir in CNA3005 experienced worsening of pre-existing depression compared with none in the indinavir arm. The background rates of pre-existing depression were similar in the 2 treatment arms

Abacavir Once Daily Versus Abacavir Twice Daily (CNA30021): Treatment-emergent clinical adverse reactions (rated by the investigator as at least moderate) with a greater than or equal to 5% frequency during therapy with abacavir 600 mg once daily or abacavir 300 mg twice daily both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily from CNA30021, were similar. For hypersensitivity reactions, subjects receiving abacavir once daily showed a rate of 9% in comparison with a rate of 7% for subjects receiving abacavir twice daily. However, subjects receiving abacavir 600 mg once daily experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared with subjects who received abacavir 300 mg twice daily. Five percent (5%) of subjects receiving abacavir 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects receiving abacavir 300 mg twice daily. Two percent (2%) of subjects receiving abacavir 600 mg once daily had severe diarrhea while none of the subjects receiving abacavir 300 mg twice daily had this event.

Laboratory Abnormalities: Laboratory abnormalities (Grades 3 to 4) in therapy-naive adults during therapy with abacavir 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and Efavirenz 600 mg daily from CNA30024 are listed in Table 7.

Table 7. Laboratory Abnormalities (Grades 3 to 4) in Therapy-naive Adults (CNA30024) through 48 Weeks of Treatment

Grade 3/4 Laboratory Abnormalities	Abacavir plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Elevated CPK (>4 X ULN)	8%	8%
Elevated ALT (>5 X ULN)	6%	6%
Elevated AST (>5 X ULN)	6%	5%
Hypertriglyceridemia (>750 mg/dL)	6%	5%
Hyperamylasemia (>2 X ULN)	4%	5%
Neutropenia (ANC <750/mm^3)	2%	4%
Anemia (Hgb ≤6.9 gm/dL)	<1%	2%
Thrombocytopenia (Platelets <50,000/mm^3)	1%	<1%
Leukopenia (WBC ≤1,500/mm^3)	<1%	2%

ULN = Upper limit of normal.

n = Number of subjects assessed.

Laboratory abnormalities in CNA3005 are listed in Table 8.

Table 8. Treatment-emergent Laboratory Abnormalities (Grades 3 to 4) in CNA3005

	Abacavir plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Elevated CPK (>4 x ULN)	18 (7%)	18 (7%)
ALT (>5 x ULN)	16 (6%)	16 (6%)
Neutropenia (<750/mm^3)	13 (5%)	13 (5%)
Hypertriglyceridemia (>750 mg/dL)	5 (2%)	3 (1%)
Hyperamylasemia (>2 x ULN)	5 (2%)	1 (<1%)
Hyperglycemia (>13.9 mmol/L)	2 (<1%)	2 (<1%)
Anemia (Hgb ≤6.9 g/dL)	0 (0%)	3 (1%)

ULN = Upper limit of normal.

n = Number of subjects assessed.

The frequencies of treatment-emergent laboratory abnormalities were comparable between treatment groups in CNA30021

Clinical Trials Experience in Pediatric Subjects

Therapy-experienced Pediatric Subjects (Twice-daily Dosing)

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or equal to 5% frequency during therapy with abacavir 8 mg per kg twice daily, lamivudine 4 mg per kg twice daily, and zidovudine 180 mg per m^2 twice daily compared with lamivudine 4 mg per kg twice daily and zidovudine 180 mg per m^2 twice daily from CNA3006 are listed in Table 9.

Table 9. Treatment-emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4, Greater than or Equal to 5% Frequency) in Therapy-experienced Pediatric Subjects (CNA3006) through 16 Weeks of Treatment

Adverse Reaction	Abacavir plus Lamivudine plus Zidovudine (n = 102)	Lamivudine plus Zidovudine (n = 103)
Fever and/or chills	9%	7%
Nausea and vomiting	9%	2%
Skin rashes	7%	1%
Ear/nose/throat infections	5%	1%
Pneumonia	4%	5%
Headache	1%	5%

Laboratory Abnormalities: In CNA3006, laboratory abnormalities (anemia, neutropenia, liver function test abnormalities, and CPK elevations) were observed with similar frequencies as in a trial of therapy-naive adults (CNA30024). Mild elevations of blood glucose were more frequent in pediatric subjects receiving abacavir (CNA3006) as compared with adult subjects (CNA30024).

Other Adverse Events

In addition to adverse reactions and laboratory abnormalities reported in Tables 2, 3, 4, 5, and 6, other adverse reactions observed in the expanded access program were pancreatitis and increased GGT.

Additional Pediatric use information for patients aged 3 months and above is approved for ViiV Healthcare Company's ZIAGEN® (abacavir sulfate) tablets and oral solution. However, due to ViiV Healthcare Company's marketing exclusivity rights, this drug product is not labeled with that paediatric information.

Post marketing Experience

The following adverse reactions have been identified during post marketing use of abacavir. Because these reactions are reported voluntarily from a population of unknown size, it is not

always possible to reliably estimate their frequency or establish a causal relationship to drug exposures

Body as a Whole

Redistribution/accumulation of body fat.

Cardiovascular

Myocardial infarction.

Hepatic

Lactic acidosis and hepatic steatosis

Skin

Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

There have also been reports of erythema multiforme with abacavir use.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the authority ADR reporting tool; search for authority Adverse Reactions Reporting Tool in the Google Play Store;

4.9 Overdose

There is no known specific treatment for overdose with abacavir. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5′-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA.

Antiviral Activity

The antiviral activity of abacavir against HIV-1 was assessed in a number of cell lines including primary monocytes/macrophages and peripheral peripheral blood mononuclear cells (PBMCs). EC_{50} values ranged from 3.7 to 5.8 μM (1 microM = 0.28 mcg per mL) and 0.07 to 1 microM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and the mean EC_{50} value was 0.26 ± 0.18 microM against 8 clinical isolates. The median EC_{50} values of abacavir were 344 nM (range: 14.8 to 676 nM), 16.9 nM (range: 5.9 to 27.9 nM), 8.1 nM (range: 1.5 to 16.7 nM), 356 nM (range: 35.7 to 396 nM), 105 nM (range: 28.1 to 168 nM), 47.6 nM (range: 5.2 to 200 nM), 51.4 nM (range: 7.1 to 177 nM), and 282 nM (range: 22.4 to 598 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC_{50} values against HIV-2 isolates (n = 4), ranged from 0.024 to 0.49 microM. The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir. Ribavirin (50 microM) used in the treatment of chronic HCV infection had no effect on the anti–HIV-1 activity of abacavir in cell culture.

Resistance

HIV-1 isolates with reduced susceptibility to abacavir have been selected in cell culture. Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated subjects demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I emerged in HIV-1 RT. M184V or I substitutions resulted in an approximately 2-fold decrease in susceptibility to abacavir. Substitutions K65R, L74M, or Y115F with M184V or I conferred a 7- to 8-fold reduction in abacavir susceptibility, and combinations of three substitutions were required to confer more than an 8-fold reduction in susceptibility.

Thirty-nine percent (7 of 18) of the isolates from subjects who experienced virologic failure in the abacavir once-daily arm had a greater than 2.5-fold mean decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5 to 11) compared with 29% (5 of 17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7 to 13).

Cross-Resistance

Cross-resistance has been observed among NRTIs. Isolates containing abacavir resistance-associated substitutions, namely, K65R, L74V, Y115F, and M184V, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, and tenofovir in cell culture and in subjects. An increasing

number of thymidine analogue mutation substitutions (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

5.2 Pharmacokinetic properties

Pharmacokinetics in Adults

The pharmacokinetic properties of abacavir were independent of dose over the range of 300 to 1,200 mg per day.

Absorption and Bioavailability: Following oral administration, abacavir is rapidly absorbed and extensively distributed. The geometric mean absolute bioavailability of the tablet was 83%. Plasma abacavir AUC was similar following administration of the oral solution or tablets. After oral administration of 300 mg twice daily in 20 subjects, the steady-state peak serum abacavir concentration (Cmax) was 3 ± 0.89 mcg per mL (mean ± SD) and AUC(0 to 12 h) was 6.02 ± 1.73 mcg•hour per mL. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, Cmax was 4.26 ± 1.19 mcg per mL (mean ± SD) and AUC∞ was 11.95 ± 2.51 mcg•hour per mL.

Distribution: The apparent volume of distribution after IV administration of abacavir was 0.86 ± 0.15 L per kg, suggesting that abacavir distributes into extravascular space. In 3 subjects, the CSF AUC (0 to 6 h) to plasma abacavir AUC (0 to 6 h) ratio ranged from 27% to 33%.

Binding of abacavir to human plasma proteins is approximately 50% and was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes.

Metabolism and Elimination: In humans, abacavir is not significantly metabolized by cytochrome P450 enzymes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5′-carboxylic acid and glucuronyl transferase to form the 5′-glucuronide. The metabolites do not have antiviral activity. In vitro experiments reveal that abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant concentrations.

Elimination of abacavir was quantified in a mass balance trial following administration of a 600-mg dose of 14C-abacavir: 99% of the radioactivity was recovered, 1.2% was excreted in the urine as abacavir, 30% as the 5′-carboxylic acid metabolite, 36% as the 5′-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal elimination accounted for 16% of the dose.

In single-dose trials, the observed elimination half-life (t1/2) was 1.54 ± 0.63 hours. After intravenous administration, total clearance was 0.80 ± 0.24 L per hour per kg (mean ± SD).

Effects of Food on Oral Absorption

Bioavailability of abacavir tablets was assessed in the fasting and fed states with no significant difference in systemic exposure (AUC∞); therefore, abacavir tablets may be administered with or without food. Systemic exposure to abacavir was comparable after administration of abacavir oral solution and abacavir tablets. Therefore, these products may be used interchangeably.

Special Populations

Renal Impairment: The pharmacokinetic properties of abacavir have not been determined in patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of elimination in humans.

Hepatic Impairment: The pharmacokinetics of abacavir have been studied in subjects with mild hepatic impairment (Child-Pugh Class A). Results showed that there was a mean increase of 89% in the abacavir AUC and an increase of 58% in the half-life of abacavir after a single dose of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver disease; however, the rates of formation and elimination of the metabolites were decreased

Pediatric Patients: The pharmacokinetics of abacavir have been studied after either single or repeat doses of abacavir in pediatric subjects. Subjects receiving abacavir oral solution according to the recommended dosage regimen achieved plasma concentrations of abacavir similar to adults. Subjects receiving abacavir oral tablets achieved higher plasma concentrations of abacavir than subjects receiving oral solution.

Additional pediatric use information for patients aged 3 months and above is approved for ViiV Healthcare Company's ZIAGEN® (abacavir sulfate) tablets and oral solution. However, due to ViiV Healthcare Company's marketing exclusivity rights, this drug product is not labeled with that pediatric information

Geriatric Patients: The pharmacokinetics of abacavir have not been studied in subjects older than 65 years.

Gender: A population pharmacokinetic analysis in HIV-1-infected male (n = 304) and female (n = 67) subjects showed no gender differences in abacavir AUC normalized for lean body weight

Race: There are no significant or clinically relevant racial differences between blacks and whites in abacavir pharmacokinetics.

Drug Interactions

In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms (2C9, 2D6, 3A4). Based on these data, it is unlikely that clinically significant drug interactions will occur between abacavir and drugs metabolized through these pathways.

Lamivudine and/or Zidovudine: Fifteen HIV-1-infected subjects were enrolled in a crossover-designed interaction trial evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

5.3 Preclinical safety data

Carcinogenicity

Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose of 600 mg.

Mutagenicity

Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an *in vivo* mouse bone marrow micronucleus assay.

Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Impairment of Fertility

Abacavir did not affect male or female fertility in rats at a dose associated with exposures approximately 8 times higher than the exposure in humans at the dose of 600 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline cellulose, Sodium starch glycolate, Colloidal silicon dioxide, Magnesium stearate.

Coating: Opadry Yellow (13K52177)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Container pack: 60s HDPE container

6.6 Special precautions for disposal

No special requirements for disposal

7. APPLICANT/MANUFACTURER

7.1 Name of the Applicant:

Name	:	**M/s. Hetero Labs Limited,**
Business Address	:	7-2-A2, Hetero Corporate, Industrial Estates, Sanath Nagar, Hyderabad-500 018 Telangana, INDIA
Telephone	:	+91-040-23704923/24/25
Fax	:	+91-040-23704926

7.2 Name and Address of Manufacturer

Name	:	HETERO LABS LIMITED Unit-III, 22-110, I.D.A., Jeedimetla, Hyderabad - 500 055, Telangana, INDIA.